

## REMARKS

Applicants respectfully request reconsideration of the present application.

## CLAIMS STATUS

Applicants have amended claim 21 to correct an inadvertent typographical error and claim 26 to present the claimed subject matter in a clearer manner. Support for amended claim 26 may be found throughout the specification as filed and, in particular, on page 4, lines 9-11. No new matter has been added.

Applicants have added new claims 50-52. Support for the new claims may be found throughout the specification as filed and, in particular, for claims 50-51 on page 4, lines 9-11; and for claim 52 on pages 2-3. No new matter has been added.

After the amendment, pending claims include a) examined claims 11-14, 17-18 and 21-26; b) withdrawn claims 15-16, 19-20 and 27-49; and c) new claims 50-52, which are readable on the elected species of the elected group and, thus, should be examined in the present application.

## CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶ 2

Claims 11-14, 17-18 and 21-26 stands rejected as indefinite. Applicants respectfully traverse.

Amended claim 21 depends on claim 11. Accordingly, Applicants believe that the present amendment obviates the indefiniteness rejection as formulated in paragraph bridging pages 3-4 of the Office Action.

As for the issue of “a subject in need thereof”, Applicants respectfully submit that one of ordinary skill would know that the term “a subject in thereof” refers to a subject to whom pulmonary administration may be beneficial. Accordingly, Applicants request withdrawal of the rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶ 1

Claim 26 stand rejected as failing to comply with the written description requirement. Applicants respectfully traverse.

Applicants respectfully submit that amended claim 26 recites an inhalable agent, which is prostacyclin or a derivative thereof. Applicants respectfully submit that one of ordinary skill in the art would have concluded that Applicants were in possession of the invention because, at the time the present application was filed, a limited number of inhalable derivatives of prostacyclin were known. Applicants respectfully submit that examples of such inhalable prostacyclin derivatives include iloprost and treprostinil.

In sum, Applicants respectfully request withdrawal of the rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 11-13, 17-18 and 21-25 stand rejected as obvious over Mihalko et al. (U.S. Patent No. 5,340,587) in view of Webb et al. (U.S. Patent No. 5,814,335) in view of Hunt et al. (Am. J. Respir Crit Care Med 2000; 161:694-699). Applicants respectfully traverse.

Applicants respectfully submit that the PTO failed to establish a *prima facie* case of obviousness.

Mihalko relates to a method and system for treating bronchial constriction diseases, such as asthma, emphysema, bronchitis and bronchiectasis, see abstract, column 1, lines 40-42. Mihalko's system includes a liposomes composition containing a  $\beta_2$ -adrenoreceptor agonist in a liposome-entrapped form, and a device for aerolizing a metered quantity of the composition, see abstract. According to Mihalko,  $\beta_2$ -adrenoreceptor agonists are, in general, uncharged, water soluble, and relatively small molecules. In his working examples, Mihalko discloses studies for one particular  $\beta_2$ -adrenoreceptor agonist, which is metaproteranol sulfate (MPS), which is encapsulated in multilamellar vesicle (MLV) liposomes of various lipid compositions, which all included one neutral PC phospholipid. In Example III, Mihalko uses in his drug efflux studies among other liposome compositions the following two liposome compositions, each of which contains both DPPC and CH lipids: a) DPPC/CH/ $\alpha$ -T (6:4:0.1)

MLV liposomes encapsulating MPS, see Table 4, and b) DPPC/DPPG/CH/ $\alpha$ -T (5:1:1:0.1) MLV liposomes encapsulating MPS. In Example IV, Mihalko examines the effect on liposome integrity of aerolizing an aqueous liposome suspensions for four liposome compositions, among which is preparation #3 (DPPC/DPPG/CH/ $\alpha$ -T (5:1:4:0.1)), which contains both DPPC and CH lipids. Applicants respectfully submit that the above mentioned Example's III DPPC/CH/ $\alpha$ -T (6:4:0.1) and DPPC/DPPG/CH/ $\alpha$ -T (5:1:1:0.1) compositions as well as DPPC/DPPG/CH/ $\alpha$ -T (5:1:4:0.1) are the only three liposome compositions disclosed in Mihalko that contain both DPPC and CH lipids.

Applicants respectfully submit that none of Mihalko's liposome compositions contains sphingomyelin. Furthermore, nowhere in his disclosure Mihalko mentions sphingomyelin as a possible component for his liposome compositions. The PTO explicitly admits these deficiencies of Mihalko on page 8 of the Office Action by stating "Mihalko does not teach that the liposome further comprises sphingomyelin".

To remedy the admitted deficiencies of Mihalko, the PTO relies on Webb and Hunt. In particular, the PTO combines a) Webb's Example 1, where Webb compares acid stability of distearoylphosphatidylcholine (DSPC) /Cholesterol (Chol) liposomes vs sphingomyelin (SM) /Cholesterol (Chol) liposomes and finds that SM/Chol liposomes are more stable to acid hydrolysis than DSPC/Chol at pH 4.0 and b) Hunt's finding that the components of lungs afflicted by asthma are more acidic than those of healthy lungs and concludes as follows:

"It would have been *prima facie* obvious for one of ordinary skill in the art to have modified the liposome used in the method taught by Mihalko et al. to further include sphingomyelin in view of the teachings of Webb and Hunt. One would have been motivated to do so because as taught by Webb, sphingomyelin increases the hydrolysis stability of cholesterol containing liposomes to acid hydrolysis; and further, as taught by Hunt et al. components of the lung afflicted with asthma are more acidic than those of healthy lung. Thus, one of skill in the art would have a reasonable expectation of success that by modifying the liposome used in the method taught by Mihalko et al. to further include sphingomyelin in view of the teachings of Webb and Hunt, one

would achieve a liposome having increased [stability] to acid hydrolysis for the treatment of diseases associated with bronchial constriction," Office Action, paragraph bridging pages 8-9.

Applicants respectfully submit that the PTO failed to establish a *prima facie* of obviousness at least for the following reasons:

1) One of ordinary skill in the art would not have concluded that suggested by the PTO inclusion of sphingomyelin in any of three of Mihalko's DPPC and CH-containing liposome compositions would predictably increase their stability to acid hydrolysis because Mihalko's liposomes are multilamellar vesicle liposomes, while Webb's SM/Chol and DSPC/Chol liposome are large unilamellar liposomes, which is a type of liposomes, which is different from Mihalko's multilamellar vesicle liposomes. Applicants respectfully submit that the PTO does not provide any documentary evidence demonstrating that hydrolysis stability of multilamellar liposomes can be predicted from the stability of unilamellar liposomes. Applicants respectfully submit that, without such evidence, Webb's results can at most be applicable only to unilamellar liposomes and, thus, one of ordinary skill in the art would not extrapolated Webb's results to multilamellar vesicle liposomes. Thus, for this reason alone, one of ordinary skill in the art would not be motivated to modify Mihalko's liposome compositions to arrive at the liposome compositions disclosed in the pending claims.

2) Applicants respectfully submit that even if for the argument's sake only, Mihalko's liposome compositions and Webb's liposome compositions were of the same type, i.e. if they both were either multilamellar vesicle liposomes or unilamellar liposomes, one of ordinary skill in the art would still not be motivated to modify Mihalko's DPPC and CH-containing liposome compositions as asserted by the PTO to arrive at the liposome compositions recited in the pending claims because Webb teaches away from such modification. Applicants respectfully submit that Mihalko requires a presence of PC lipids, such as DPPC or DSPC lipids, in his liposome compositions. Applicants further submit that Webb's results demonstrate that SM/Chol liposome composition, which is a cholesterol containing liposome composition that includes sphingomyelin but does not include PC lipids, is more stable to acid hydrolysis than DSPC/Chol, which is a cholesterol containing liposome composition that includes PC lipids, but does not include sphingomyelin. Applicants respectfully submit that,

Webb's results teach away from the suggested by the PTO modification of Mihalko's liposome compositions, because in view of Webb's results, one of ordinary skill in the art would rather be motivated to replace PC lipids in Mihalko's compositions with sphingomyelin, instead of adding sphingomyelin to PC lipids as suggested by the PTO.

3) Applicants respectfully submit that one of ordinary skill in the art would not have concluded that acid hydrolysis stability of SM/Chol liposome compositions studied by Webb is relevant for treating bronchial constriction because acidic conditions of Webb and Hunt do not overlap. Applicants respectfully submit that Webb tests acidic hydrolysis stability of his compositions at pH 2.0 and 4.0. At the same time, Hunt results demonstrate pH of deaerated exhaled airway condensate in patients with acute asthma is  $5.23 \pm 0.21$ , with the lowest single patient pH value well above 4.0, see Hunt, abstract and Figure 1. In view of the lack of the overlap between Hunt's and Webb's value, the logic on which the PTO relied in its obviousness rejection is deficient at least for this reason.

In sum, because the PTO failed to establish a *prima facie* case of obviousness, Applicants request withdrawal of the rejection.

Claims 26 stands rejected as obvious over Mihalko et al. (U.S. Patent No. 5,340,587) in view of Webb et al. (U.S. Patent No. 5,814,335) in view of Hunt et al. (Am. J. Respir Crit Care Med 2000; 161:694-699) further in view Morton Jr. et al. (U.S. Patent No. 4,732,914). Applicants respectfully traverse.

Applicants discussed the deficiencies of Mihalko, Hunt and Webb above. Morton does not cure these deficiencies. Thus, because the PTO failed to establish a *prima facie* case of obviousness, Applicants request withdrawal of the rejection.

#### NEW CLAIMS 50-52

New claims 50-52 are patentable over the cited references at least because these claim depend on patentable claim 11.

#### CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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